REMARKS

Claims 44-46 AND 49-52 are pending in this application. The present rejections to the claims are respectfully traversed. Claims 44-46 and 52 have been amended for clarity.

Withdrawn Objections and/or Rejections

Applicants note with appreciation that the rejection of claims 39-43 and 50-51 under 35 U.S.C. § 112, first paragraph regarding inadequate written description is withdrawn.

Applicants note with appreciation that the alternative rejection of claims 39-46 and 49-51 under 35 U.S.C. § 102(a) as being anticipated by Wood et al., (WO99/14328) is withdrawn.

Information Disclosure Statement

Applicants thank the Examiner for considering the Information Disclosure Statement submitted 17 October 2003.

Correction of Inventorship

Applicants note that the Examiner has indicated that the inventorship in this application has been changed. Applicants note that they have yet to receive a corrected filing receipt.

Rejections under 35 U.S.C. § 101 and 112, first paragraph

Claims 44-46 and 49-52 stand rejected under 35 U.S.C. § 101 because the claimed invention is allegedly not supported by a credible, specific and substantial asserted utility or a well established utility.

Claims 44-46 and 49-52 stand rejected also under 35 U.S.C. § 112, first paragraph. Specifically since the claimed invention is allegedly not supported by either a credible, specific and substantial asserted utility or a well established utility, one skilled in the art would allegedly not know how to use the claimed invention.

Previously Applicant had provided section 1.132 declarations of Audrey Goddard and Avi Ashkenazi discussing the gene amplification assay. The Patent Office indicates that the gene amplification assay provides a patentable utility for the PRO 269 nucleic acid.

The Patent Office indicates that the Ashkenazi declaration is not of record in the instant application. Applicants filed the Ashkenazi declaration with their Response on 17 October 2003. A copy of the stamped postcard listing the declaration in enclosed. However, Applicants again enclose the declaration and request that it be made of record.

The Patent Office indicates that the gene amplification assay does not establish a utility for PRO269 polypeptides, to which this application is directed. For the reasons outlined below, Applicants respectfully disagree. With respect to claims 44-46 and 49-52, Applicants submit that not only has the Patent Office not established a *prima facie* case for lack of utility and enablement, but that the PRO269 polypeptides possess a credible, specific and substantial asserted utility and are fully enabled.

Evidentiary Standard

An Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re* Langer, 503 F.2d 1380,1391, 183 USPQ 288, 297 (CCPA 1974); *see, also In re* Jolles, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re* Irons, 340 F.2d 974, 144 USPQ 351 (1965); *In re* Sichert, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977).

Compliance with 35 U.S.C. § 101 is a question of fact. Raytheon v. Roper, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration. *In re* Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992) Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the PTO must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Only after the PTO has made a proper *prima facie* showing of lack of utility, does the

burden of rebuttal shift to the applicant. The issue will then be decided on the totality of evidence.

A *prima facie* case of lack of utility has not been established

The Patent Office bases its conclusion that gene amplification does not reliably correlate with increased mRNA transcript or polypeptide levels, and hence its conclusion that PRO269 polypeptides lack utility, on Pennica *et al.*, Konopka *et al.*, and Haynes *et al.*

The Patent Office cites Pennica *et al.* to support its argument that gene amplification does not reasonably correlate with increased mRNA or polypeptide levels. According to the Patent Office, Pennica *et al.* teaches that "[a]n analysis of *WISP*-1 gene amplification and expression in human colon tumors *showed a correlation between DNA amplification and over-expression,* . . . . In contrast, *WISP*-2 DNA was amplified in colon tumors, but its mRNA expression was significantly reduced in the majority of tumors compared with expression in normal colonic mucosa from the same patient." (Emphasis added). Applicants submit that the Patent Office has omitted to disclose that in the same paragraph, Pennica *et al.* also explains that the reason for the absence of correlation between amplification and over-expression may be because the gene while initially believed to be amplified, was not in fact amplified — "it is possible that the *apparent* amplification observed for *WISP-2* may be caused by another gene in this amplicon." Emphasis added. Accordingly, Applicants respectfully submit that Pennica *et al.* teaches nothing conclusive regarding the absence of correlation between amplification of a gene and over-expression of the encoded polypeptide. Further, Applicants do not claim that the utility of the instant invention is the over-expression of *WISP-2* mRNA.

The Patent Office also cites the abstract of Konopka *et al.* to establish that "[p]rotein expression is not related to amplification of the *abl* gene . " Applicants respectfully submit that Applicants do not claim that the utility of the instant invention is the over-expression of the *abl* gene.

Lastly, the Patent Office cites Haynes *et al.*, to show that there was a "general trend but no strong correlation between protein [expression] and transcript levels" for 80 *yeast* proteins. Haynes *et al.*, adds that "[f]or **some** genes, equivalent mRNA levels translated into protein abundances which varied by more than 50-fold." (Emphasis added).

Haynes *et al.* is directed to a study of normally expressed genes in the yeast *Saccharomyces cerevisiae*. Haynes *et al.* identified 80 protein spots which correlated to highly abundant proteins in the cell. There are approximately 6000 gene products in yeast. Haynes *et al.* indicated that they were only able to visualize and identify the more abundant proteins. "Since many important regulatory proteins are present only at low abundance levels these would not be amenable to analysis using such techniques". The statement made by Haynes *et al.* cannot be applied to the current application. Haynes *et al.* was not studying expression in human cells and his system was only able to detect the most abundant proteins which are not the important regulatory proteins. Finally, Haynes was not looking at the overexpression of proteins in tumor cells.

Based on the above, the Patent Office concludes that increased copy number does not *necessarily* result in increased protein expression. The standard, however, is not absolute certainty. The fact that in the case of a specific class of closely related molecules there seemed to be no correlation with gene amplification and the level of mRNA/protein expression, does not establish that it is more likely than not, in general, that such correlation does not exist.

The PTO has not shown whether the lack of correlation between gene amplification and polypeptide over-expression observed for WISP-2 polypeptides, or the abl gene, or some genes in a family of 80 yeast genes is typical, or is merely a discrepancy, an exception to the rule of correlation. Indeed, the working hypothesis among those skilled in the art is that, if a gene is amplified in cancer, the encoded protein is likely to be expressed at an elevated level. In fact, as noted even in Pennica *et al.*, *a correlation between DNA amplification and over-expression of polypeptide* ***was observed*** *in the case of WISP-1*. Similarly, Haynes *et al.*, state that **some** genes **did** show a correlation between increased mRNA levels and translated protein.

Even if a *prima facie* case of lack of utility has been established, it should be withdrawn on consideration of the totality of evidence

Even if it is more likely than not that there is no correlation between gene amplification and increased mRNA/protein expression, which Applicants specifically deny, a polypeptide encoded by a gene that is amplified in cancer would **still** have a credible, specific and

substantial utility. In support, Applicants herewith submit a Declaration by Avi Ashkenazi, Ph.D., an expert in the field of cancer biology and an inventor of the instant application. Dr. Avi Ashkenazi's Declaration explains that:

> even when amplification of a cancer marker gene does not result in significant over-expression of the corresponding gene product, this very absence of gene product over-expression still provides significant information for cancer diagnosis and treatment. Thus, if over-expression of the gene product does not parallel gene amplification in certain tumor types but does so in others, then parallel monitoring of gene amplification and gene product over-expression enables more accurate tumor classification and hence better determination of suitable therapy. In addition, absence of over-expression is crucial information for the practicing clinician. If a gene is amplified but the corresponding gene product is not over-expressed, the clinician accordingly will decide not to treat a patient with agents that target that gene product.

Applicants thus submit that simultaneous testing of gene amplification and gene product over-expression enables more accurate tumor classification, even if the gene-product, the protein, is not over-expressed. This leads to better determination of a suitable therapy. Further, as explained in Dr. Ashkenazi's Declaration, absence of over-expression of the protein itself is crucial information for the practicing clinician. If a gene is amplified in a tumor, but the corresponding gene product is not over-expressed, the clinician will decide not to treat a patient with agents that target that gene product. This not only saves money, but also the patient need not be exposed to the side effects associated with such agents.

This is further supported by the teachings of the attached article by Hanna and Mornin[1]. The article teaches that the HER-2/neu gene has been shown to be amplified and/or over-expressed in 10%-30% of invasive breast cancers and in 40%-60% of intraductal breast carcinoma. Further, the article teaches that diagnosis of breast cancer includes testing both the amplification of the HER-2/neu gene (by FISH) as well as the over-expression of the HER-2/neu gene product (by IHC). Even when the protein is not over-expressed, the assay relying on both tests leads to a more accurate classification of the cancer and a more effective treatment of it.

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[1] Copy enclosed.

Thus, Applicants have demonstrated a credible, specific and substantial asserted utility for the PRO269 polypeptide, for example, in detecting over-expression or absence of expression of PRO269. Further, based on this utility and the disclosure in the specification, one skilled in the art at the time the application was filed would know how to use the claimed polypeptides.

Priority

1. Applicants have asserted priority to PCT International Application No. PCT/US00/03565, filed February 11, 2000

Applicants have previously asserted priority to PCT International Patent Application No. PCT/US00/03565 filed February 11, 2000. This application discloses the PRO269 gene and includes the DNA amplification assay data found in the current application.

The Patent Office has denied the priority claim on the basis that the priority application allegedly lacks utility and enablement for the reasons set forth in the rejection of the instant application. The Patent Office has determined the effective filing date for the instant claims to be 12 July 2001.

Applicants submit that, for the reasons set forth above, the results of the gene amplification assay (Example 92) in PCT/US00/03565 provide specific, substantial and credible utility for the polypeptide PRO269 in this invention. For the reasons set forth above, the PRO269 polypeptide is also fully enabled.

2. Applicants have also asserted priority to PCT Patent Application No. PCT/US98/19330, Wood et al., filed 16 September 1998.

Applicants have also asserted priority to PCT Patent Application No. PCT/US98/19330, Wood et al., filed 16 September 1998 in the original declaration filed. Applicants submit that PCT Patent Application No. PCT/US98/19330 simply needs to provide a disclosure commensurate in scope with the disclosure in the cited art to support the priority claim.

In *In re* Stempel (1957) 113 USPQ 77, the patent applicant (Stempel) had claims directed to both (i) a particular genus of chemical compounds (the "generic" claim) and (ii) a single species of chemical compound that was encompassed within that genus (the "species" claim). In support of a rejection under 35 U.S.C. § 102, the examiner cited against the Stempel application a prior art reference that disclosed the exact chemical compound recited in Stempel's "species" claim. In response to the rejection, Stempel filed a declaration under 37 C.F.R. §. 1.131 demonstrating that he had made that specific chemical compound prior to the effective date of the cited prior art reference. The CCPA found Stempel's 131 declaration effective for swearing behind the cited reference for purposes of both the "species" claim and the "genus" claim. Specifically, the CCPA stated in support of its decision:

"We are convinced that under the law all the applicant can be required to show [in a declaration under 37 C.F.R. §. § 1.131] is priority with respect to **so much of the claimed invention as the reference happens to show**. When he has done this he has disposed of the reference." (Id. at 81; emphasis supplied).

Secondly, the Examiner is respectfully directed to *In re* Moore, 170 USPQ 260 (CCPA 1971), where the Stempel rule was extended to cases where a reference disclosed the claimed compound but failed to disclose a sufficient utility for it. More specifically, the patent applicant (Moore) claimed a specific chemical compound called PFDC. In support of a rejection of the claim under 35 U.S.C. § 102, the examiner cited a reference which disclosed the claimed PFDC compound, but did not disclose a utility for that compound. Applicant Moore filed a declaration under 37 C.F.R. § 1.131 demonstrating that he had made the PFDC compound before the effective date of the cited prior art reference, even though he had not yet established a utility for that compound. On appeal, the CCPA indicated that the 131 declaration filed by Moore was sufficient to remove the cited reference. The CCPA relied on the established "Stempel Doctrine" to support its decision, stating:

An applicant need **not** be required to show [in a declaration under 37 C.F.R. § 1.131] any more acts with regard to the subject matter claimed that can be carried out by one of ordinary skill in the pertinent art following the description contained in the reference....the determination of a practical utility when one is not obvious need **not** have been accomplished prior to the date of a reference unless the reference also teaches how to use the compound it describes. (Id. at 267, emphasis supplied).

Thus, *In re* Moore confirms the Stempel rule holding that in order to effectively remove a cited reference with a declaration under 37 C.F.R. § 1.131, an applicant need only show that portion of his or her claimed invention that appears in the cited reference.

Applicants have claimed priority to PCT Patent Application No. PCT/US98/19330, Wood et al., filed 16 September 1998. Applicants maintain that they should be entitled to priority to this application to remove prior art references with similar disclosures consistent with the teachings of *In re* Stempel and *In re* Moore.

Rejections under 35 U.S.C. §102

1. Claims 44-46 and 49-52 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Wood et al., WO99/14328 (PCT/US98/19330).

A. Applicants are claiming priority to to PCT Application No. PCT/US00/03565 filed 11 February 2000. Wood et al. was published less than one year prior to the effective filing date of the present invention. Accordingly, Wood et al. is not a 35 U.S.C.102(b) prior art reference.

B. Applicants are also claiming priority to PCT Application No. PCT/US98/19330 filed 16 September 1998 (the same reference being cited as prior art). For the reasons set forth above, Wood et al. is removed as a 35 U.S.C. 102(b) prior art reference.

Withdrawal of this rejection is respectfully requested.

2. Claims 39-43 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Valenzuela et al., WO00/11015 (published 2 March 2000). Valenzuela et al. teaches a polypeptide with allegedly 100% sequence identity to PRO269.

A. Applicants have claimed priority to PCT Application No. PCT/US00/03565 filed 11 February 2000. Accordingly, Valenzuela et al. is not prior art since its effective date is after the effective date of the present application.

B. Applicants have claimed priority to Wood et al. (WO99/14328) filed 16 September 1998. The Patent Office has stated that Wood et al. (WO99/14328) (to which Applicants claim priority) teaches the PRO269 polypeptide Therefore Wood et al. teaches what is taught by Valenzuela. Accordingly, Valenzuela et al. is not prior art since its effective date is after the effective date of the present application of 16 September 1998

Withdrawal of this rejection is respectfully requested.

CONCLUSION

It is submitted that the present application is in form for allowance, and such action is respectfully requested.

The Commissioner is authorized to charge any additional fees which may be required, including petition fees and extension of time fees, to Deposit Account No. 08-1641 (Docket No.39780-1618 P2C33).

Respectfully submitted,

Date: May 21, 2004

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TECHNICAL UPDATE

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HER-2/neu Breast Cancer Predictive Testing

Julie Sanford Hanna, Ph.D. and Dan Mornin, M.D.

EACH YEAR, OVER 182,000 WOMEN in the United States are diagnosed with breast cancer, and approximately 45,000 die of the disease.[1] Incidence appears to be increasing in the United States at a rate of roughly 2% per year. The reasons for the increase are unclear, but non-genetic risk factors appear to play a large role.[2]

Five-year survival rates range from approximately 65%-85%, depending on demographic group, with a significant percentage of women experiencing recurrence of their cancer within 10 years of diagnosis. One of the factors most predictive for recurrence once a diagnosis of breast cancer has been made is the number of axillary lymph nodes to which tumor has metastasized. Most node-positive women are given adjuvant therapy, which increases their survival. However, 20%-30% of patients without axillary node involvement also develop recurrent disease, and the difficulty lies in how to identify this high-risk subset of patients. These patients could benefit from increased surveillance, early intervention, and treatment.

Prognostic markers currently used in breast cancer recurrence prediction include tumor size, histological grade, steroid hormone receptor status, DNA ploidy, proliferative index, and cathepsin D status. Expression of growth factor receptors and over-expression of the HER-2/neu oncogene have also been identified as having value regarding treatment regimen and prognosis.

HER-2/neu (also known as c-erbB2) is an oncogene that encodes a transmembrane glycoprotein that is homologous to, but distinct from, the epidermal growth factor receptor. Numerous studies have indicated that high levels of expression of this protein are associated with rapid tumor growth, certain forms of therapy resistance, and shorter disease-free survival. The gene has been shown to be amplified and/or overexpressed in 10%-30% of invasive breast cancers and in 40%-60% of intraductal breast carcinoma.[3]

There are two distinct FDA-approved methods by which HER-2/neu status can be evaluated: immunohistochemistry (IHC, HercepTest™) and FISH (fluorescent in situ hybridization, PathVysion™ Kit). Both methods can be performed on archived and current specimens. The first method allows visual assessment of the amount of HER-2/neu protein present on the cell membrane. The latter method allows direct quantification of the level of gene amplification present in the tumor, enabling differentiation between low- versus high-amplification. At least one study has demonstrated a difference in recurrence risk in women younger than 40 years of age for low- versus high-amplified tumors (54.5% compared to 85.7%); this is compared to a recurrence rate of 16.7% for patients with no HER-2/neu gene amplification.[4] HER-2/neu status may be particularly important to establish in women with small ($\leq$1 cm) tumor size.

The choice of methodology for determination of HER-2/neu status depends in part on the clinical setting. FDA approval for the Vysis FISH test was granted based on clinical trials involving 1549 node-positive patients. Patients received one of three different treatments consisting of different doses of cyclophosphamide, Adriamycin, and 5-fluorouracil (CAF). The study showed that patients with amplified HER-2/neu benefited from treatment with higher doses of adriamycin-based therapy, while those with normal HER-2/neu levels did not. The study therefore identified a sub-set of women, who because they did not benefit from more aggressive treatment, did not need to be exposed to the associated side effects. In addition, other evidence indicates that HER-2/neu amplification in node-negative patients can be used as an independent prognostic indicator for early recurrence, recurrent disease at any time and disease-related death.[5] Demonstration of HER-2/neu gene amplification by FISH has also been shown to be of value in predicting response to chemotherapy in stage-2 breast cancer patients.

Selection of patients for Herceptin© (Trastuzumab) monoclonal antibody therapy, however, is based upon demonstration of HER-2/neu protein overexpression using HercepTest™. Studies using Herceptin© in patients with metastatic breast cancer show an increase in time to disease progression, increased response rate to chemotherapeutic agents and a small increase in overall survival rate. The FISH assays have not yet been approved for this purpose, and studies looking at response to Herceptin© in patients with or without gene amplification status determined by FISH are in progress.

In general, FISH and IHC results correlate well. However, subsets of tumors are found which show discordant results; i.e., protein overexpression without gene amplification or lack of protein overexpression with gene amplification. The clinical significance of such results is unclear. Based on the above considerations, HER-2/neu testing at SHMC/PAML will utilize immunohistochemistry (HercepTest©) as a screen, followed by FISH in IHC-negative cases. Alternatively, either method may be ordered individually depending on the clinical setting or clinician preference.

CPT code information

HER-2/neu via IHC

88342 (including interpretive report)

HER-2/neu via FISH

88271×2 Molecular cytogenetics, DNA probe, each
88274 Molecular cytogenetics, interphase in situ hybridization, analyze 25-99 cells
88291 Cytogenetics and molecular cytogenetics, interpretation and report

Procedural Information

Immunohistochemistry is performed using the FDA-approved DAKO antibody kit, Herceptest©. The DAKO kit contains reagents required to complete a two-step immunohistochemical staining procedure for routinely processed, paraffin-embedded specimens. Following incubation with the primary rabbit antibody to human HER-2/neu protein, the kit employs a ready-to-use dextran-based visualization reagent. This reagent consists of both secondary goat anti-rabbit antibody molecules with horseradish peroxidase molecules linked to a common dextran polymer backbone, thus eliminating the need for sequential application of link antibody and peroxidase conjugated antibody. Enzymatic conversion of the subsequently added chromogen results in formation of visible reaction product at the antigen site. The specimen is then counterstained; a pathologist using light-microscopy interprets results.

FISH analysis at SHMC/PAML is performed using the FDA-approved PathVysion™ HER-2/neu DNA probe kit, produced by Vysis, Inc. Formalin fixed, paraffin-embedded breast tissue is processed using routine histological methods, and then slides are treated to allow hybridization of DNA probes to the nuclei present in the tissue section. The Pathvysion™ kit contains two direct-labeled DNA probes, one specific for the alphoid repetitive DNA (CEP 17, spectrum orange) present at the chromosome 17 centromere and the second for the HER-2/neu oncogene located at 17q11.2-12 (spectrum green). Enumeration of the probes allows a ratio of the number of copies of chromosome 17 to the number of copies of HER-2/neu to be obtained; this enables quantification of low versus high amplification levels, and allows an estimate of the percentage of cells with HER-2/neu gene amplification. The clinically relevant distinction is whether the gene amplification is due to increased gene copy number on the two chromosome 17 homologues normally present or an increase in the number of chromosome 17s in the cells. In the majority of cases, ratio equivalents less than 2.0 are indicative of a normal/negative result, ratios of 2.1 and over indicate that amplification is present and to what degree. Interpretation of this data will be performed and reported from the Vysis-certified Cytogenetics laboratory at SHMC.

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